For my daughters: February 2, 2021

The Coronavirus Pandemic

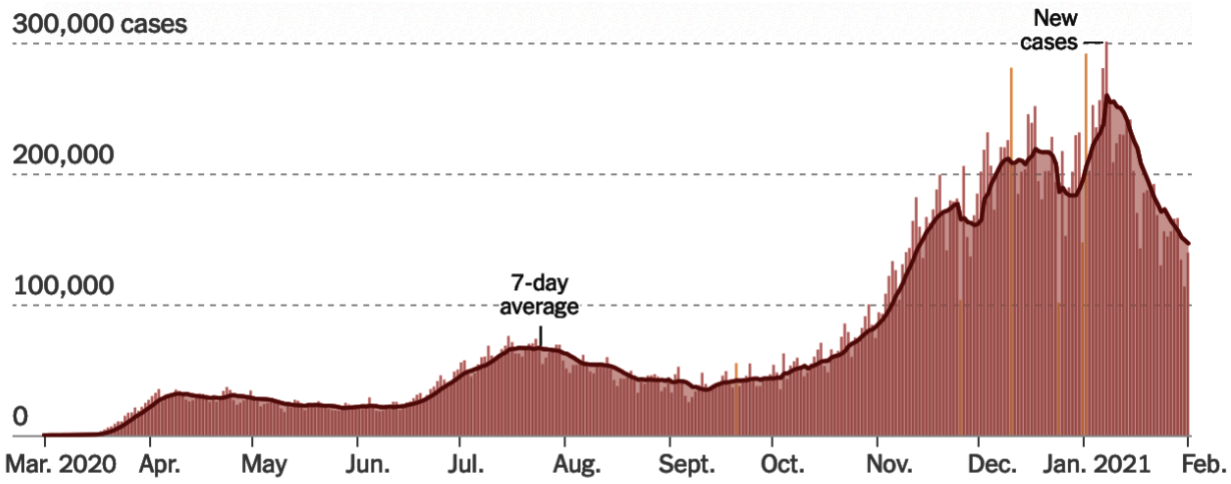
Uncertain Times

Its hard to believe it's been only a month since last I wrote. So much has happened NOT related to the coronavirus pandemic that major COVID-19 changes recede into the background noise. We have had an insurrection, an inauguration, and an impeachment. I can honestly tell the three of you I have not seen things this unsettled since I was your age and facing Vietnam.

While all this was going on, in the background three pandemic developments have been having important consequences: 1. The rate of new infections has begun to fall; 2. Vaccines are becoming available; 3. New variant forms of the virus are emerging.

Over the Hump

First development – Falling rate of new infection. We left the pandemic in my letter to you girls a month ago with a question: What course would the pandemic take in coming months? As I wrote that letter, new cases were being reported at the scary rate of 250,000 a day. With Christmas and New Year's social mixing, the fear was that we would be looking at even higher levels of infection. Well, as it turns out, that didn't happen. After briefly rising to 300,000 new cases a day that first week of January, the rate of infection in the United States has fallen steadily ever since. We are today looking at 139,293 new cases a day, and fewer each week. While today's rate of infection still a very high number and deaths in the United States due to COVID-19 will soon pass half a million, it is impossible not to be a little more hopeful.



	TOTAL REPORTED	ON FEB. 1	14-DAY CHANGE
Cases	26.3 million+	139,293	-29% ↘
Deaths	443,275	1,990	-2% →

The Vaccines Are Here

Second development - Arrival of vaccines. I have been telling you girls for months to be patient, that the vaccines are coming but would not likely be available to us until April or May. That long delay will probably not be necessary. I trot down to a local hospital day after tomorrow to get my first shot of Pfizer vaccine. Being an old guy, I was first in line, but I am hopeful not too many weeks separate mom and you girls from your shots.

As of today, 26.2 million people have been vaccinated nationwide, 7.9% of the entire population. While there is a lot of gripping about the slow pace of the rollout (our home state of Missouri is dead last among the 50 states in % of its citizens vaccinated), the new federal administration seems to be taking matters more seriously.

Five vaccines developed to combat COVID-19 are available in this country now or soon will be. Two (*Pfizer & Moderna*) are FDA-approved and have begun distribution. Another (*Oxford/AstraZenica*) has been approved in the UK and is being distributed there, although the FDA has requested its USA Phase Three clinical trials be extended to clarify the data. The other two vaccines (*Johnson & Johnson, Novavax*) are just now completing clinical trials.

Nucleic Acid Vaccines. Inject a solution containing spike-gene mRNA molecules into patient. This approach has never been used before, anywhere in the world.

- *Pfizer/BioNTech*. 95% effective at blocking sickness. A potential problem is that the vaccine must be kept ultra-cold. Requires two shots delivered a month apart.
- *Moderna/NIAD*. 94% effective at blocking sickness & 100% at preventing severe illness. Can be stored in a refrigerator. Also requires two shots.

Recombinant Vector Vaccines. Insert the COVID-19 gene for spike protein into a harmless virus and infect patient with it.

- *Oxford/AstraZenica* 62% effective at blocking infection (90% effective when given with a low initial dose). Very stable, and cheap to make. Two shots required.
- *Johnson & Johnson*. 66% effective at blocking infection (72% v. USA variant; 57% v. South African variant B.1.351), but 85% effective at blocking severe illness. A single shot.

Subunit Vaccines. Inject actual COVID-19 proteins into patient. The vaccine injects virus spike proteins, manufactured in moth cells and then attached like studs to a synthetic nanoparticle.

- *Novavax*. 96% effective v. strain found in USA and 89% effective v. British variant B.1.1.7, but only 49% effective v. South African variant B.1.351. Requires two shots.

New Variants

Third development – Emergence of new variants. A new form of COVID-19 has recently emerged in Britain. To understand it and other new forms of COVID-19 (what we will call "variants") we need to look at life from the point of view of the virus. So let's put ourselves in the shoes of a coronavirus (its spikes, if you will) and go infect a human.

Every coronavirus has protein spikes sticking out from its surface in all directions. At the tip of each spike is a portion of the protein that bumps into anything the virus encounters.

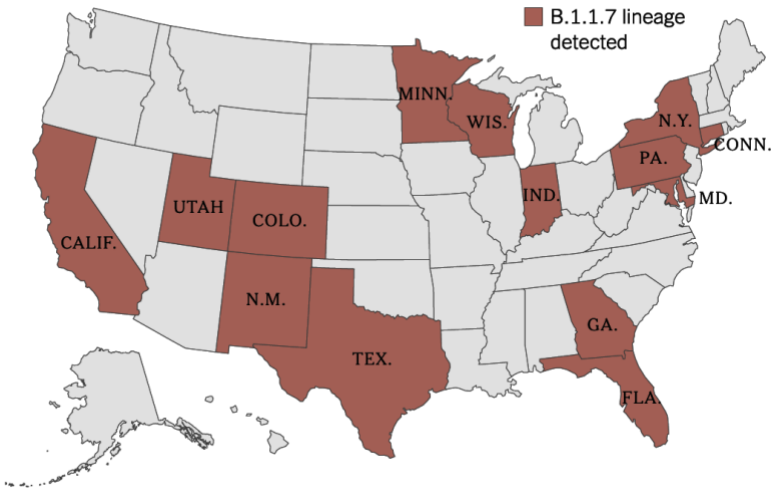
Bumping into a human cell normally doesn't have any more consequence than bumping into a brick wall – BUT, if what the tip bumps into is a human cell surface receptor called ACE2, the spike tip can slide right into a slot in the ACE2 surface, like a hand into a glove. When this happens, the spike twists in reaction, triggering the ACE2 receptor to twist in response, and in doing so literally dragging the virus into the cell. That is how infection happens. The cells lining the human lung are rich in ACE2 receptors. That is where infection happens.

Once inside a human cell, the coronavirus releases its genes – its RNA molecule – into the cell interior. There the human genetic machinery goes to work producing thousands of baby viruses. But sometimes a mistake is made (what we call a mutation) and a wrong letter is selected. Imagine copying the word "infection" mistakenly using the letter "f" instead of "j" to write instead "injection – a mutation is that sort of thing. Some viruses like flu and HIV make a lot of mistakes; coronaviruses make far fewer. Still, looking worldwide, COVID-19 acquires around two single-letter mutations a month. Now imagine a tree that branches twice a month and let it do so for a year – you are looking at several thousand different forms! We call these forms "variants."

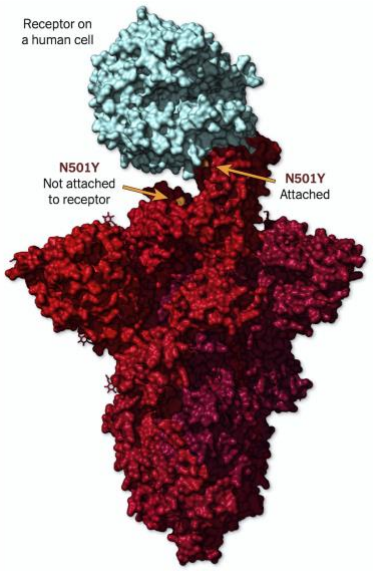
If that mutation-induced difference harms the virus in any way, the variant will simply fail to infect other humans and so quickly disappear. However, any variant better able to infect human cells will proceed to do so, and become more common. So as the pandemic proceeds, we must expect new variants to keep popping up, for the simple unavoidable reason that the virus is reproducing, and mistakes happen. Some of these variants, unfortunately, will prosper.

Rapidly-Spreading Variants

So what are these thousands of variants like? Most are unremarkable. However, in last month's letter I described to you girls a COVID-19 variant that arose in November in England called B.1.1.7. This variant renders the coronavirus quite a bit more transmissible, and so has very rapidly become more common in England. Over here, too -- at least 14 of the 50 states of our country have reported cases (we don't monitor strains as well as the British and most other countries do, so its hard to be sure how rapidly the B.1.1.7 variant has spread here). This variant does not make you any sicker – it just makes it a bit easier for you to become infected.



The British variant is one of three rapidly-spreading variants that have arisen in the last few months in the UK, South Africa, and Brazil. The variants are about 50% more contagious than what we have been dealing with in the United States. All three of these rapid spreaders share a mutation called N501Y that affects the tip of the spike protein (red below). This tip is what the virus uses to grab onto human cells at cell projections called ACE2 receptors (blue below) to trigger the virus's entry into the human cell. The N501Y mutation in these COVID-19 variants mistakenly inserts the base U where it should have added an A. This changes the 501st amino acid of the spike protein from asparagine to tyrosine, twisting the spike protein a little bit and so allowing it to bind more tightly to ACE2. This tighter binding makes infection easier, leading to the increased rate of transmission.



Nor is N501Y the only mutation we see in these three fast-spreading variants. Each variant has fully eight or ten mutations in the spike protein!

Vaccine Escape

Do you see the problem? All of the vaccines being developed to combat COVID-19 target the spike protein. Are the many changes to the spike protein in these rapid-spread variants enough to evade antibody protection? Can the variants escape our vaccines?

The clinical trials of the *Pfizer* and *Moderna* vaccines were carried out before the new rapid-spreading variants appeared. However, the three other new vaccines are just completing their Phase Three clinical trials, and a disturbing pattern has become evident: vaccines tested against the South African variant (called B.1.351) are markedly less effective. Thus the *Novavax* vaccine, 96% effective against the COVID-19 strain common in the USA, is only 49% effective v. the South African variant; the *Johnson & Johnson* vaccine is only 57% effective against it.

Could the South African B.1.351 variant also escape vaccines like *Pfizer's* and *Moderna's* which were targeted against earlier versions of the spike protein? To answer this question, Scientists in South Africa have examined blood samples from 44 survivors of COVID-19, who would have developed antibodies against the earlier version of the spike protein. They tested the potency of these antibodies against the B.1.351 variant: antibodies from 21 of the 44 patients were not capable of neutralizing the virus! That's 48% effectivity.

This doesn't bode well for vaccinated individuals in the United States. The South African variant has already been reported in several states, and this is with very little genome testing that would allow us to detect it. Shutting off travel from South Africa (but not by U.S. citizens) is not going to keep the virus out. B.1.351 is here already and it will spread rapidly. Imposing a travel ban now is shutting the barn door after the horses have run out.

So what all this tells me is that we are looking at a booster shot in the fall. Re-engineering the vaccines to deal with B.1.351 is no big deal, assuming federal authorities do not impose undue regulatory hurdles.

It appears our pandemic is not going to go away quietly this summer. Like influenza, coronavirus is with us to stay, new variants arising each year. Like our annual flu shot, we will be going to our local pharmacy for our COVID shot. Not a perfect solution, but a whole lot better than what we have now: 100 million people have contracted COVID-19 in the last 13 months, 26 million of them in this country, and 440,000 Americans have died. A shot once a year seems a small price to pay for escaping out from under that black cloud.

Sticking Close to Home

In the meantime, as we await our vaccination turn, it will be important not to lose sight of the essentials. We are still surrounded, each of us, by a virus that takes no prisoners. No one has told these virus particles that the party is almost over. Any one of us could still be made quite ill by COVID-19 infection next week. So face masks and social distancing are still crucial. Beware the temptation to get together with friends as Spring approaches. Today is Groundhog Day, but it's not at all clear to me that Dr Fauci will be able to see his shadow.

Stay safe. Remember the important things in life – like toilet paper!

Dad